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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT

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1612

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

The amendment dated 4-27-09 is acknowledged.

Claims included in the prosecution are 19-35.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 19-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant introduces the negative limitation, "wherein the method is conducted without the use of a surfactant other than the phospholipid and without ***intense*** mechanical treatment; this limitation has no support in the specification as originally filed and therefore, deemed to be new matter.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 19-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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It is unclear as to what applicant considers as 'intense' as recited in claim 19 last line.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 34 recites the broad recitation essence, and the claim also recites eye essence, which is the narrower statement of the range/limitation. This rejection is maintained since applicant has not adequately addressed this issue.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 29, 31-35 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/17523 of record.

WO teaches liposomal skin compositions containing triterpenoids, ursolic acid (page 1, lines 20-31). The method of preparation involves dissolving ursolic acid, phosphatidylcholine in ethanol and then adding this mixture to water (page 11, line 1-8, 15-19; page 16, lines 15-18; Example 1). The amounts given in millimolar quantities appear to fall within the range claimed. Product by process claims are still considered as product claims and the burden is upon applicant to show that the product claimed is different from the prior art product.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that this rejection is based upon a misunderstanding of the claims at issue; according to applicant, the claims are directed to preparing triterpenoid-containing liposomes and are directed to methods and in contrast, the claims appear to be examined as "product-by-process. This argument is not persuasive since contrary to applicant's arguments, these claims are indeed 'product-by-process' claims. Claim 29 recites, "Triterpenoid liposomes prepared by 'he method according to claim 19 and therefore, the rejected claims are product by process claims and applicant has not shown that the product of the prior art is different from instant product.

Claim Rejections - 35 USC § 103

6. . The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

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to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 19-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination with Cauwenbergh (5,476,853), Hauser (4,619,794) by themselves or in combination.

Touitou discloses a method of preparation of liposomes containing lipophilic active agents, which includes terpenes. The method involves adding the lipophilic drug and Phospholipon in ethanol-propylene glycol either at room temperature or at 60 to 70 degrees, adding to distilled water and TEA (triethanolamine) and cooling the mixture (abstract; col. 1, lines 8-32; col. 1, line 66 through col. 3, line 10; col. 4, lines 14-50; columns 5 and 6 and claims). Instant method differs from Touitou in the following way. In instant method the terpenoid is dispersed in polyol (propylene glycol) at 60-70 degrees to which TEA is added and then phospholipid solution in ethanol is added. To this mixture, water is then added. In Touitou, the lipophilic drug, phospholipid are added together in ethanol-propylene glycol mixture to which the TEA and water is added. Since the function of the base is to elevate the pH of a dispersion to alkaline values and since the addition of water to the phospholipid in the organic solvent in both Touitou and instant method, it would have been obvious to one of ordinary skill in the art at the time the invention was made to vary the steps in the method of Touitou and still expect the formation of the liposomes. Touitou also differs from instant method in the last step; that is, the addition of the acid to change the alkaline pH of the liposomal suspension. However, since the preparations of Touitou are meant for the topical application of skin,

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it would have been obvious to one of ordinary skill in the art to change the alkaline pH resulting from the addition of TEA in Touitou to neutral or near neutral pH by the addition of an acid since these pH levels are compatible with skin. One of ordinary skill in the art would be motivated to change the alkaline pH of Touitou to pH of 5 to 7.5 since the reference of Cauwenbergh while disclosing liposomal skin formulations such as toilet waters and skin milk teaches that the final pH of 5 to 7.5 is preferable and this pH can be obtained by the addition of either a base or an acid or buffer such as citric acid or phosphoric acid or acetate buffer (abstract; col. 3, lines 37-65; Examples 4 and 5). Although Touitou does not teach specifically triterpenoids and claimed triterpenoids, since he teaches generic 'terpenes', it would have been obvious to one of ordinary skill in the art to use any terpene including claimed triterpenes since these are also lipophilic with a reasonable expectation of success.

Hauser discloses methods of preparation of liposomes containing encapsulated drugs. One of the methods of preparation involves hydration at an alkaline pH of about 12 and followed by lowering the pH to 7-8 (Example 2).

One of ordinary skill in the art would be motivated to use a higher pH first and then lower the pH with a reasonable expectation of success since such a technique is routinely practiced in liposomal art as evident from Hauser.

Applicant's arguments have been fully considered, but are not persuasive. Applicant once again argues that the object of the present invention is to provide liposomes containing triterpenoid at a high concentration while using non-toxic solvent without intensive mechanical treatment and In order to incorporate triterpenoid at a high

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concentration uniformly into a liposome, the present invention employs triterpenoid having acid group, and by adding a base, the triterpenoid is transformed into its salt having surface activity. The transformed triterpenoid salt is a surfactant of high HLB, and it forms a mixed micelle system when mixed with low HLB lipid. According to applicant, by adding an acid to decrease its pH to 5-8, the triterpenoids salt transforms back to the original form having an acid group, and thereby loses its surface activity and results in changing the mixed micelle system into a liposome. Applicant argues that Touitou merely disclose(s) the use of TEA in the example of a gel preparation, but it does not disclose the reason why TEA is added to the gel preparation. Applicant further argues that Touitou does not disclose the combined use of base and triterpenoid to convert the acid moiety into its salt having surface activity as to form mixed micelle system with low HLB lipid. This argument is not persuasive since as pointed out in the previous action, the percentage of drugs encapsulated in Touitou is 3 % as evident from the examples. Instant claims recite a range of 0.0001 to 5% of the drug and it is unclear as to how this can be considered as high encapsulation. Applicant's argument that Cauwenbergh discloses that the final pH of 5-7.5 of a skin formulation is preferable and this pH can be obtained by the addition of either a base or an acid or buffer and that Cauwenbergh discloses pH regulation of a skin formulation containing liposomes merely in order to be compatible with skin, not pH regulation in the preparation of liposomes is not persuasive since motivation need not be the same as applicant's. Furthermore, the reference of Houser shows the hydration at an alkaline pH followed by lowering the pH

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to 7-8. Applicant has shown no unexpected results by modifying the method taught by Touitou.

7. Claims 19-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination with Cauwenbergh (5,476,853), Hauser (4,619, 794) (individually or in combination) as set forth above, in further combination with Delrieu (5,962,015).

The teachings of Touitou and Cauwenbergh have been discussed above.

Delrieu while disclosing stabilized liposome formulations teaches that compounds such as triethanolamine, a common cosmetic buffer, can be added to phospholipid starting materials during the preparation of the liposomes to prevent aggregation and provide some stability (abstract, col. 2, lines 2-5). Therefore, one of ordinary skill in the art to add TEA after instant step A with a reasonable expectation of success since Delrieu teaches that TEA can be added at any state of liposome preparation.

Applicant's arguments with regard to Touitou, Cauwenbergh and Hauser have already been addressed by the examiner. Applicant argues that the use of TEA in Delrieu is to prevent aggregation which is different from that of the present invention. This argument is not persuasive since as pointed out above, the motivation to use TEA need not be the same as applicants.

8. Claims 19-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination with Cauwenbergh (5,476,853), Hauser (4,619, 794) (individually or in combination) or these references in further combination

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with Delrieu (5,962,015) as set forth above, further in view of WO 01/17523 of record or vice versa: that is, WO 01/17523 in view of Touitou by itself or in combination with either Cauwenbergh, Hauser or Delrieu.

The teachings of Touitou, Cauwenbergh and Hauser have been discussed above.

WO teaches liposomal skin compositions containing triterpenoids, ursolic acid (page 1, lines 20-31). The method of preparation involves dissolving ursolic acid, phosphatidylcholine in ethanol and then adding this mixture to water (Example 1). WO however, does not teach the inclusion of propylene glycol or prepare the liposomes by the addition of TEA.

The use of ursolic acid as the terpene in the generic teachings of Touitou or in the teachings of Touitou, Cauwenbergh and Delrieu with a reasonable expectation of success since WO teaches that ursolic acid can be encapsulated in liposomes for skin treatment. Alternately, the use of the method of Touitou in WO would have been obvious to one of ordinary skill in the art since according to Touitou the ethosomes prepared by the method taught are softer and have enhanced skin permeability for various compounds (col. 2, lines 3-24).

Applicant provides no specific arguments regarding this rejection and therefore, the rejection is maintained.

9. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination with Cauwenbergh (5,476,853), Hauser (4,619,

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794) (individually or in combination) or these references in further combination with Delrieu (5,962,015) as set forth above, further in view of WO 01/17523 of record or vice versa: that is, WO 01/17523 in view of Touitou by itself or in combination with either Cauwenbergh, Hauser or Delrieu further in view of Hayashi (US 4,606,911).

The teachings of Touitou, Cauwenbergh, Hauser, Delrieu and WO have been discussed above. What is lacking in these references is the use of liposomal triterpenoids in tooth paste.

Hayashi teaches that triterpenoids are useful in the prevention of dental carries and suggests compositions in the form of tooth-paste (Examples and claims).

The use of the terpenoids in the form of tooth-pastes in the teachings of Touitou, Hauser, Cauwenbergh, Delrieu and WO would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Hayashi teaches the effectiveness of terpenoids in the prevention of dental carries.

Applicant provides no specific arguments regarding this rejection and therefore, the rejection is maintained.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK